REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1-5, 10-11 and 21-31 are currently pending in this application. In this amendment, claims 29-31 are amended, and claim 26 is canceled. Claims 1-5, 10-11, 21-25 and 27-31 will be pending following entry of this amendment.

Claim 1 is amended to recite "100 to 3330 nucleotides in length" and to delete the term "at least 95%". Support is provided in the specification at, *e.g.*, paragraphs [143] and [114], and in SEQ ID NO:1.

Claims 29-31 are amended to delete the term "exactly" for clarity.

Claim 31 is amended to correct a typographical error.

No new matter is added by these amendments.

II. The Presently Claimed Invention

Applicants have identified and cloned an extracellular interphotoreceptor matrix (IPM) proteoglycan, IPM 150. IPM proteoglycans, such as IPM 150, play important roles in the human neural retina, acting as adhesive elements bridging the interface between the retinal pigment epithelium and the retina. Changes in IPM proteoglycans are associated with ocular diseases and disorders such as retinal detachment, chorioretinal degeneration, and macular degeneration. For example, linkage between a mutated form of IPM 150 and a human ocular disease has been reported (Lith-Verhoeven *et al.*, *Invest Ophthalmol Vis Sci* 45:30-35, 2004; copy provided in the response filed September 7, 2005), and allelic variation in the rhesus macaque IPM 150 gene shows strong association with retinal drusen formation (Singh *et al.*, *Exp Eye Res* 81:401-406, 2005; copy provided in the supplemental communication filed November 16, 2005).

The present claims are directed to IPM 150 polynucleotides. The claimed polynucleotides may be used, *inter alia*, as probes or primers to detect alterations or abnormalities in level of expression, composition and/or sequence of IPM 150 polynucleotides in various ocular diseases and disorders. Useful as a diagnostic, the claimed polynucleotides may also be used to produce IPM 150 polypeptides, which can be used to generate anti-IPM 150 antibodies. The antibodies may be used, for example, for histological staining of the retina, for purification of IPM 150 proteoglycans, and for detection of IPM 150 polypeptides and fragments in body fluids. Such antibodies would be more useful than antibodies directed against chondroitin sulfate to detect alterations or abnormalities in level of expression, composition and/or sequence of IPM 150 polypeptides in various ocular diseases and disorders. See, *e.g.*, paragraphs 21 to 22.

To avoid possible confusion, Applicants would like to draw the Office's attention to paragraphs 47 to 50 of the specification. It should be noted that the polynucleotide of SEQ ID NO:1 does not encode the IPM 150 isoform A polypeptide of SEQ ID NO:2. This is because SEQ ID NO:1 consists of exons 1 through 17 of the IPM 150 gene, and the insertion of exon 5B, which is 62 bases in length, between exons 5 and 6. As a result, the polynucleotide encoded by SEQ ID NO:1 corresponds to the IPM 150 isoform C polypeptide of SEQ ID NO:6, and not the IPM 150 isoform A polypeptide of SEQ ID NO:2. This is due to the presence of an in-frame stop codon in exon 5B. See paragraph 50 for details. Alternatively, a polynucleotide of SEQ ID NO:1 and lacking exon 5B encodes the IPM 150 isoform A polypeptide of SEQ ID NO:2.

III. Written Description Rejection

Claims 1-5, 10-11 and 21-31 were rejected as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection to the extent it may be applied to the claims as amended.

The Office acknowledges that the specification describes the polynucleotide of SEQ ID NO:1 and the polynucleotide encoding SEQ ID NO:2, but asserts that the specification

does not disclose all polynucleotides at least 95% identical to SEQ ID NO:1, all possible fragments, primers and probes of SEQ ID NO:1, and all polynucleotides encoding a polypeptide comprising at least 190 contiguous amino acids of SEQ ID NO:2.

As an initial matter, the claims now pending are directed to sequences identical or complementary to SEQ ID NO:1, and not to sequences at least 95% identical to SEQ ID NO:1. Thus, the issue here is whether the specification provides adequate written description for fragments, primers and probes of SEQ ID NO:1, and nucleotide sequences encoding polypeptide fragments of SEQ ID NO:2.

To the extent that the Office is concerned with the activity of the claimed polynucleotides or encoded polypeptides, there is no requirement that the claimed polynucleotides encode a polypeptide with the biological activity of the naturally occurring protein. The polynucleotide and polypeptide sequences provided in the specification are clearly "identifying characteristics" sufficient to support the pending claims.

Applicants believe that it is clear that the skilled artisan, provided with the sequences of the IPM 150 polynucleotides and polypeptides and guided by the specification, would be able to envision all of the claimed species of IPM 150 polypeptide fragments, probes and primers, and polynucleotides encoding IPM 150 polypeptides. In addition, the specification would be unwieldy in length if Applicants were required to specify each and every nucleic acid sequence intended to be covered by the claims. The specification provides adequate written description for the claimed genus because it discloses the complete sequences of the IPM150 cDNA and the IPM 150 isoform A polypeptide (SEQ ID NOs:1 and 2, respectively), as well as various lengths of IPM 150 polynucleotide fragments, probes and primers of SEQ ID NO:1.

For example, the specification provides the nucleotide sequences and encoded polypeptide sequences for three isoforms (A, B and C) of IPM 150 and one variant of IPM 150 isoform A. The sequence of the claimed IPM 150 polynucleotide is recited in SEQ ID NO:1, and IPM 150 isoform A polypeptide is recited in SEQ ID NO:2. The specification also describes

IPM 150 polynucleotides of different sizes. For example, the specification discloses: IPM 150 fragments, *e.g.*, at least 15, 20, 25, 29, 31, 35, 50, 75, 100, 150, 200, 215, 216 ,217, 218, 250, 300, 350, 400, 450, 500, 539, 540, 541, 542, 550, 750, 1000, 1500, 2000, or more of SEQ ID NO:1; IPM 150 probes and primers, *e.g.*, at least 10, 12, 15, 18, 25, 50, or 100 bases of SEQ ID NO:1, or between 12 and 100, between 12 and 50, or between 12 and 25 bases of SEQ ID NO:1; and polynucleotides encoding the IPM 150 polypeptide and fragments thereof of SEQ ID NO:2. See, *e.g.*, paragraphs 143, 145, 148, 150, 151 and 158.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1-5, 10-11, 21-25 and 27-31 as lacking written description be withdrawn.

IV. Enablement Rejection

Claims 1-5, 10-11 and 21-31 were rejected as allegedly not enabled. Applicants respectfully traverse this rejection to the extent it may be applied to the claims as amended.

The Office acknowledges that the specification is enabling for the polynucleotide of SEQ ID NO:1 and for polynucleotides encoding the polypeptide of SEQ ID NO:2, but alleges that the specification does not reasonably provide enablement for all polynucleotides at least 95% identical to SEQ ID NO:1, all possible fragments, primers and probes of SEQ ID NO:1, and all polynucleotides encoding polypeptide fragments of 190 contiguous amino acids of SEQ ID NO:2.

Again, as an initial matter, the claims, as amended, are directed to sequences identical or complementary to SEQ ID NO:1, and not to sequences at least 95% identical to SEQ ID NO:1. Thus, the issue here is whether the specification is enabled for fragments, primers and probes of SEQ ID NO:1, and for nucleotide sequences encoding polypeptides of SEQ ID NO:2.

It is routine in the art to make polynucleotides of various lengths or composition once the DNA sequence is known. Here, Applicants disclose the sequences of the IPM 150

polynucleotide (SEQ ID NO:1) and the IPM 150 isoform A polypeptide (SEQ ID NO:2), and describe methods to make and use the claimed polynucleotides.

The test for enablement is whether one reasonably skilled in the art could make and use the invention, without undue experimentation, using disclosures in the specification coupled with information known in the art. The skilled artisan, guided by the specification and using routine techniques known in the art, would be able to make polynucleotide fragments, probes and primers of SEQ ID NO:1 and polynucleotides encoding polypeptides of SEQ ID NO:2. The skilled artisan, guided by the specification and using routine techniques known in the art, would also be able to use the claimed polynucleotides, *e.g.*, as probes or primers in screening assays to detect alterations or abnormalities in level of expression, composition and/or sequence of IPM 150 polynucleotides. Because changes in IPM proteoglycan composition correlate with proper retinal adhesion and the etiology of photoreceptor demise, the detection of IPM 150 polynucleotides is useful for analyzing IPM proteoglycan expression in various ocular diseases and disorders. The skilled artisan would also be able to use the claimed polynucleotides to produce IPM 150 polypeptides to generate anti-IPM 150 antibodies, which can be used for histological staining of the retina, for purifying IPM 150 proteogylcans, or for detecting IPM 150 polypeptides and fragments in body fluids. Because IPM 150 sequence changes are known to be associated with disease, IPM 150 polynucleotide probes and anti-IPM 150 antibodies are useful for monitoring and for diagnosing various ocular diseases and disorders.

The Office alleges that "the specification does not provide working examples of different DNA sequences that would enable a representative number of the above discussed DNA sequences with assurances that they can be used to encode the protein of interest" and that "there is but a single polynucleotide disclosed with reference to IPM 150 isoform A, SEQ ID NO:2." Applicants disagree. The specification provides working examples in addition to the IPM 150 polynucleotide of SEQ ID NO:1. For examples, paragraph 285 teaches a primer complementary to nucleotides 2927 to 2943 of SEQ ID NO:27, which corresponds to nucleotides 2996 to 3012 of SEQ ID NO:1, used to reverse transcribe human retinal RNA. Paragraph 338

teaches a cDNA fragment spanning bases 1636 to 2241 of SEQ ID NO:27, which corresponds to bases 1701 to 2306 of SEQ ID NO:1, used to make a probe for *in situ* hybridization. Paragraph 345 teaches a cDNA probe corresponding to nucleotides 817 to 3160 of SEQ ID NO:27, which corresponds to nucleotides 882 to 3229 of SEQ ID NO:1. In addition, the specification describes the cloning of IPM 150 polynucleotides that are encompassed by the pending claims. See, *e.g.*, paragraphs 291, 292 and 293. Accordingly, the specification provides working examples that enable IPM polynucleotide fragments, probes and primers such that the skilled artisan could use the claimed polynucleotides without undue experimentation.

The Office alleges that because the claims include polynucleotides as small as 12 nucleotides, the claims read on an infinite number of possible DNA sequences, so that undue experimentation would be required to enable a commensurate number of sequences. Applicants disagree. Virtually any claim using "comprising" language could be said to encompass an "infinite" number of embodiments. As explained previously, the claimed polynucleotides can be used without undue experimentation. Here, the claimed polynucleotides are characterized both by size and sequence: the polynucleotides of claim 1 comprise 100 to 3330 nucleotides identical or complementary to SEQ ID NO:1; the polynucleotides of claim 4 encode polypeptides comprising at least 190 contiguous amino acid residues of SEQ ID NO:2; and the primers or probes of claim 29 have between 12 and 100 contiguous nucleotides identical or complementary to SEQ ID NO:1. Accordingly, the claimed polynucleotides do not read on an infinite number of possible DNA sequences because they are limited in both size and sequence.

The Office next considers the protein encoded by the polynucleotides of the present invention, and alleges that undue experimentation would be required to generate the changes/modifications of the nucleotides contemplated and yet retain the function of the encoded IPM 150 variants. To the extent that the Office is concerned with the activity of the IPM 150 polypeptides encoded by the claimed polynucleotides, Applicants respectfully disagree. As explained previously, there is no requirement that the claimed polynucleotides encode IPM 150 polypeptides that retain biological function. Without agreeing with the Office, Applicants have

amended claim 1 so that the claimed polynucleotides are identical or complementary to SEQ ID NO:1. It is respectfully submitted that no undue experimentation would be required to make IPM 150 polynucleotides encoding polypeptides comprising amino acid sequences of SEQ ID NO:2. The claimed polynucleotides can be made and used without encoding a polypeptide with biological activity, *e.g.*, to produce IPM 150 polypeptides for the generation of antibodies that can be used in histological staining of the retina or to purify IPM 150 proteoglycans.

Based on the foregoing, Applicants respectfully request that the rejection of claims 1-5, 10-11, 21-25 and 27-31 as lacking enablement be withdrawn.

V. Indefiniteness Rejection.

Claims 29-31 were rejected as being indefinite.

The Office indicated that the limitation "exactly complementary" in claims 29-31 is indefinite because the Examiner understands that "complementary sequences" are by definition "exact." Applicants have amended claims 29-31 to delete "exactly", thereby obviating this rejection.

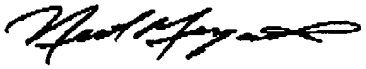
VI. Claim Objections

Claim 26 was objected to as being of improper dependent form. Applicants have canceled this claim, rendering the objection moot.

VII. Request for Interview

To expedite prosecution, Applicants respectfully request an Examiner interview. The undersigned will call the Examiner to arrange an interview once the Examiner has had a chance to review this amendment.

Respectfully submitted,



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